Express Mail Certificate No. EV298592756US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
APPLICATION FOR LETTERS PATENT

Applicants: CHING-FEN HSIAO
YI-LOONG WANG
YA-SHENG YANG
YA-CHING CHANG CHIEN

Title : SUSTAINED RELEASE TAMSULOSIN FORMULATIONS

5 Claims

2 Sheets of Drawings

William E. Pelton
Reg. No. 25,702
Donald S. Dowden
Reg. No. 20,701
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

SUSTAINED RELEASE TAMSULOSIN FORMULATIONS

BACKGROUND OF THE INVENTION

1. Field of Invention

The present invention relates to a sustained release tamsulosin formulation.

2. Description of the Related Art

The mechanism of physiological action of tamsulosin is through blocking the -receptors actions in the cells of the urethra and prostate, so that the stress of a prostate is reduced and the difficulties with the flow of urine due to hypertrophy of the prostate are alleviated.

US Patent No. 4,772,475 discloses a formulation including controlled release formulations comprising an acrylic acid polymer, an acrylic acid copolymer or a cellulose derivative. More than 50% (w/w) microcrystalline cellulose was added into an oral sustained release formulation as a release-modulating agent. However, the high concentration of microcrystalline cellulose would increase the friction when a formulation mixture is kneaded and also elevate the temperature of the formulation mixture during the process of granulation. Also, acrylic acid polymer becomes glue-like under a high temperature, and the glue-like status of acrylic acid polymers in granulation procedures is unfavorable.

There is still a need in the related art to provide a sustained release of tamsulosin formulation, which can overcome the problems of resulted from temperature increase the glue-like status of acrylic acid polymer in the process of granulation, and maintain the desired extended-release effect.

SUMMARY OF THE INVENTION

An aspect of the present invention is to provide a sustained release pharmaceutical composition of tamsulosin.

The pharmaceutical composition of the present invention contains tamsulosin or a pharmaceutical acceptable salt thereof, a hydrophobic polymer, a microsphere forming agent, and a diluent.

In a preferred embodiment of the present invention, the pharmaceutical composition contains tamsulosin or a pharmaceutical acceptable salt thereof, a hydrophobic polymer in a range from about 10% to about 65% (w/w), a microsphere forming agent in a range from about 20% to about 65% (w/w), and a diluent in a range from about 10% to about 40% (w/w).

Other aspects, advantages and novel features of the invention will become more apparent from the following detailed description when taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the bio-equivalence comparison of a conventional sustained release tamsulosin formulation and a sustained release tamsulosin formulation of the present invention;

Fig. 2 shows the dissolution profiles of a sustained release tamsulosin formulation of the present invention (test) and a conventional tamsolusin formulation (reference).

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, a sustained release tamsulosin formulation is provided.

The term "sustained release" as used herein refers to formulation or dosage units of this invention that are slowly and continuously dissolved and absorbed in the stomach and gastrointestinal tract over a period of time.

The term "microsphere forming agent" as used herein refers to any binders of this invention that are used for forming a granule. The microsphere forming agent for the present invention also uses for making the size of the granulation equalized.

The term "fluctuation" as used herein refers to the changes of the concentration of tamsulosin in a human body. A smaller fluctuation of the sustained release tamsulosin formulation refers to the concentration of tamsulosin in blood is more stable.

The term "procedures" as used herein refers to the way to mix compounds.

The term "steps" as used herein refers to the order of producing the sustained release tamsulosin formulation.

Polymers have been widely used as a matrix for sustained release formulations. Hydrophobic polymers are suitably employed in the sustained release formulation, including pH-dependent and pH-independent polymers.

To provide for a sustained release tamsulosin formulation of the present invention, hydryphobic polymers (include pH-dependent and pH-independent polymers) are chosen to control the dissolution profile of tamsilosin formulation so that the formulation releases tamsulosin slowly and continuously as the formulation passed through the stomach and gastrointestinal tract. The dissolution control capacity of such polymers is

particularly important in a sustained release tamsulosin formulation because it may cause damping effects if the tamsulosin is released too rapidly.

The hydrophobic polymers used for the invention are those which could avoid burst out of drug during its residence in the stomach and gastrointestinal tract. Many materials known as the hydrophobic polymers in the pharmaceutical art include sodium carboxymethyl cellulose, cellulose acetate, ethyl cellulose (EC), hydroxypropyl methyl-cellulose acetate succinate (HPMCAS) and cellulose acetate propionate (CAP). These polymers may be used alone or mixed in a sustained release tamsulosin formulation. The pH-dependent polymers are present in the tamsulosin formulation of this invention in an amount ranging from about 10 to about 65 wt %.

A water-soluble tamsulosin, a microsphere forming agent, a release-modulating agent and a diluent are mixed to obtain a mixture. Preferred microsphere forming agents that can be used in forming granules containing tamsulosin are glyceride or wax. Preferred release-modulating agents that can be used for delaying release rate of tamsulosin are the hydrophobic polymers. The mixture was added into a knead solution to form an oral dosage unit. An oral dosage unit of the sustained release tamsulosin formulations of this invention may be in the form of a capsule or a granule. The granules may be coated one or more films for different purposes and then encapsulated.

In preferred embodiments of the present invention, the range of the concentration of tamsulosin in the sustained release tamsulosin formulations is from about 0.03% to about 3% by weight based on the weight of the oral dosage unit (w/w). The range of the concentration of the hydrophobic polymers

in the sustained release tamsulosin formulations is about 10% to about 65% by weight based on the weight of the oral dosage unit (w/w). The hydrophobic polymers are used to lower the fluctuation of the formulation in a human body. The range of the concentration of the microsphere forming agent in the sustained release tamsulosin formulations is about 20% to about 65% by weight based on the weight of the oral dosage unit (w/w). The microsphere forming agent also has the lubricating effect and can make the procedure of granulation favorable. Also, the glue-like status of the acrylic polyol polymers under a high temperature can be improved by the use of microsphere forming agent.

The sustained release tamsulosin formulation of the present invention may also contain pharmaceutical diluent. The range of the concentration of the diluent in the sustained release tamsulosin formulation of the present invention is about 10% to about 40% by weight based on the weight of the oral dosage unit (w/w).

The preferred diluents according to the present invention could be lactose, starch, mannitol, sodium hydroxylpropyl cellulose, sodium starch, microcrystalline cellulose, glyceryl behenate, talcum powder, stearic acid, stearic salt and sodium stearyl fumarate.

The preferred microsphere forming agents according to the present invention contain glyceryl triacetate, glyceryl monostearate, glyceryl behenate, paraffin wax and carnauba wax.

A method of conducting film coating is described as follows. A film coating premix is solved in water and organic solvent. The organic solvent used for preparing the film coating premix could be alcohol, acetone or isopropanol.

Other diluents or anti-adhesive agents can be added into the above solvent mixture if necessary.

Other features and advantages of the present invention will be apparent from the following description of the preferred embodiments and from the claims.

Examples

The following examples illustrate various aspects of the present invention but do not limit the claims in any manner whatsoever.

Example 1: Sustained release tamsulosin formulation (1) and method for the production thereof

Sustained release tamsulosin formulation (1)

(a)	tamsulosin HCl	1.00 g
	microcrystalline cellulose (MC)	208.5 g
	stearic acid	58 g
	glyceryl behenate	290 g
	methacrylic copolymer	22.5g
(b)	film coat	
	sodium carboxymethyl cellulose	0.85 g
	talcum powder	27 gw
	triethyl citrate	10.5 g
	methacrylic copolymer	105.5 g

Procedures:

The sustained release tamsulosin formulations of this invention are prepared as follows:

1. Tamsulosin HCl, microcrystalline cellulose, stearic acid and glyceryl behenate are intimately mixed.

2. Methacrylic copolymer was wet-blended.

3. Film coat premix 1: sodium hydroxylpropyl cellulose, methacrylic copolymer, talcum powder and triethyl citrate were mixed well.

Steps:

1. The mixture obtained from Example 1 Procedure 1 was mixed with the mixture obtained from Example 1 Procedure 2.

2. The mixture obtained from Step 1 was put into an extruding granulator and centrifugal spheroider to form a granule.

3. The granules were dried in a tray dryer.

4. The dried granule was put into a fluidized bed coater, and the film coat premix 1 solved in the selected solvent was sprayed on an outer surface of the granule.

Example 2: Sustained release tamsulosin formulation (2) and method for the production thereof

Sustained release tamsulosin formulation (2)

ethyl cellulose (EC)	134 g
hydroxylpropyl cellulose	0.6 g
talcum powder	10.8 g
triethyl citrate	8.4 g

Procedures:

Film coat premix 2: ethyl cellulose, hydroxypropylmethyl cellulose (HPMC), talcum powder and triethyl citrate were mixed well.

Steps:

1. The granules obtained from Example 1 were put into a fluidized bed coater, and the film coat premix 2 solved in a selected solvent was sprayed on

the above granules.

Example 3: Sustained release tamsulosin formulation (3) and method for the production thereof

Sustained release tamsulosin formulation (3)

(a)	tamsulosin HCl	0.40 g
	microcrystalline cellulose (MC)	54.0 g
	hydroxypropyl methyl cellulose succinate (HPMCAS)	20.0 g
	stearic salt	2.0 g
	glyceryl behenate	134.0 g
	ethyl cellulose	98.6 g

Procedures:

1. Tamsulosin HCl, microcrystalline cellulose, hydroxypropyl methyl cellulose acetate succinate (HPMCAS), stearic salt and glyceryl behenate were mixed well.

2. Ethyl cellulose was wet-blended.

Steps:

1. The mixture obtained from Example 3 Procedure 1 was mixed with the mixture obtained from Example 3 Procedure 2.

2. The mixture obtained from Step 1 was put into an extruding granulator and centrifugal spheroider to form a granule.

Example 4: Sustained release tamsulosin formulation (4) and method for the production thereof

Sustained release tamsulosin formulation (4)

(a)	tamsulosin HCl	0.40 g
	microcrystalline cellulose (MC)	39.2 g

hydroxypropyl methyl cellulose acetate succinate (HPMCAS)	20.0 g
stearic salt	6.4 g
glyceryl behenate	120.0 g
ethyl cellulose	113.3 g

Procedures:

1. Tamsulosin HCl, microcrystalline cellulose, hydroxypropyl methyl cellulose acetate succinate (HPMCAS), stearic salt and glyceryl behenate were mixed well.

2. Ethyl cellulose was wet-blended.

Steps:

1. The mixture obtained from Example 4 Procedure 1 was mixed with the mixture obtained from Example 4 Procedure 2.

2. The mixture obtained from Step 1 was put into an extruding granulator and centrifugal spheroider to form a granule.

Example 5: Sustained release tamsulosin formulation (5) and method for the production thereof

Sustained release tamsulosin formulation (5)

(a)	tamsulosin HCl	0.40 g
	microcrystalline cellulose (MC)	39.2 g
	cellulose acetate phthalate (CAP)	20.0 g
	magnesium stearate	6.4 g
	glyceryl behenate	120.0 g
	ethyl cellulose	113.3 g

Procedures:

1. Tamsulosin HCl, microcrystalline cellulose, cellulose acetate phthalate (CAP), sterate and glyceryl behenate were mixed well.

2. Ethyl cellulose was wet-blended.

Steps:

1. The mixture obtained from Example 5 Procedure 1 was mixed with the mixture obtained from Example 5 Procedure 2.

2. The mixture obtained from Step 1 was put into an extruding granulator and centrifugal spheroider to form agranule.

Example 6: Sustained release tamsulosin formulation (6) and method for the production thereof

Sustained release tamsulosin formulation (6)

(a)	microcrystalline cellulose (MC)	39.2 g
	cellulose acetate phthalate (CAP)	20.0 g
	sterate	6.4 g
	glyceryl behenate	66.0 g
	ethyl cellulose	50.0 g
(b)	castor oil	20.0 g
	tamsulosin HCl	0.40 g
	ethyl cellulose aqueous dispersion	126.67 g

Procedures:

1. Microcrystalline cellulose, sterate, cellulose acetate phthalate (CAP), glyceryl behenate and ethyl cellulose were mixed well.

2. Tamsulosin HCl and ethyl cellulose aqueous dispersion were mixed well.

Steps:

1. The mixture obtained from Example 6 Procedure 1 was mixed with castor oil.

2. The above mixture obtained from Step 1 was mixed with Example 6 Procedure 2.

3. Then the mixture obtained from Example 6 Step 2 was put into an extruding granulator and centrifugal spheroider to form a granule.

Example 7: Sustained release tamsulosin formulation (7) and method for the production thereof

Sustained release tamsulosin formulation (7)

(a)	microcrystalline cellulose (MC)	39.2 g
	cellulose acetate phthalate (CAP)	20.0 g
	magnesium stearate	6.4 g
	glyceryl behenate	66.0 g
	ethyl cellulose	70.0 g
	tamsulosin HCl	0.40 g
	ethyl cellulose aqueous dispersion	133.33 g

Procedures:

1. Microcrystalline cellulose, cellulose acetate phthalate (CAP), sterate, glyceryl behenate and ethyl cellulose were mixed well.

2. Tamsulosin HCl and ethyl cellulose aqueous dispersion were mixed well.

Steps:

1. The mixture obtained from Example 7, Procedure 1 was mixed with the mixture obtained from Example 7 Procedure 2.

2. Then the mixture obtained from Example 7 Step 2 was put into an extruding granulator and centrifugal spheroider to form a granule.

Example 8: Bio-equivalence

Table 1:

Parameters	conventional sustained release tamsulosin	Sustained release tamsulosin formulation

	formulation	from Example 5 of the present invention
[AUC]ss(ng/ml×hr)	79.8±33.5	82.8±36.1
fluctuation	1.96±0.576	1.79±0.466
C_{ave}^{ss} (ng/ml)	3.32±1.40	3.45±1.50
C_{max}^{ss} (ng/ml)	7.72±3.35	7.28±2.70
C_{min}^{ss} (ng/ml)	1.23±0.651	1.42±0.830
T_{ave}^{ss} (hour)	5.12±1.31	3.92±1.12

Tables 2 and 3 show the bio-equivalence of the conventional sustained release tamsulosin formulation and sustained release tamsulosin formulation of the present invention based on an analysis of the blood samples from 25 individuals. Results are shown in Table 2 and Table 3, and Fig. 1 depicts the comparison of the data given in Table 2 and Table 3.

Table 2:

Time course of release of tamsulosin from a conventional sustained release tamsulosin formulation				
Time(hour)	Nos.	Average concentration (ng/ml)	Standard Deviation	C.V.(%)
72	25	1.28	0.858	67.1
96	25	1.42	0.974	68.6
120	25	1.34	0.749	55.9
144	25	1.20	0.6698	58.1
145	25	1.80	0.958	53.3
146	25	3.53	1.99	56.4
147	25	4.71	2.39	50.7
148	25	6.19	3.39	54.8
148.5	25	6.80	3.18	46.8

149	25	6.89	2.97	43.1
149.5	25	6.58	2.80	42.6
150	25	5.92	2.60	43.9
151	25	5.69	2.25	39.5
152	25	5.00	1.89	37.7
154	25	3.99	1.67	41.7
156	25	3.11	1.50	48.2
158	25	2.65	1.31	49.4
168	25	1.30	0.781	60.2

1 Table 3:

Time course of release of tamsulosin from an embodiment of the sustained release tamsulosin formulation from Example 5 of the present invention				
Time (hour)	Nos.	Average concentration (ng/ml)	Standard Deviation	C.V.(%)
72	25	1.38	0.797	60.2
96	25	1.40	0.661	47.4
120	25	1.38	0.608	44.1
144	25	1.28	0.759	59.5
145	25	3.57	1.63	45.6
146	25	5.41	2.58	47.7
147	25	5.92	2.36	39.8
148	25	6.42	2.59	40.3
148.5	25	6.67	2.78	41.6
149	25	6.18	2.38	38.5
149.5	25	5.68	2.15	37.8
150	25	5.50	2.01	36.5

151	25	4.92	2.03	41.2
152	25	4.43	2.09	47.2
154	25	3.63	1.83	50.4
156	25	2.94	1.46	49.8
158	25	2.72	1.48	54.2
168	25	1.57	0.996	63.3

The data in Table 2 and Table 3 show the fluctuations between conventional sustained release tamsulosin formulation and sustained release tamsulosin formulation obtained from the present invention. The sustained release tamsulosin formulation obtained from the present invention has a small fluctuation value, in other words, sustained release tamsulosin formulation obtained from the present invention is more suitable for patients than conventional tamsulosin form.

Example 9: Ingredient-releasing rate test

Experiments: Testing of ingredient-releasing rates of the tamsulosin medicine:

The rates of tamsulosin release from the tamsulosin formulations made according to Examples 1-7 (test) and a conventional sustained release tamsulosin formulation (reference) were evaluated in a dissolution test under the instructions of the United States Pharmacopoeia (U.S.P.) 26th edition. In this test, each tamsulosin formulation and 500ml of pH 6.8 phosphate buffer were poured into a vessel and heated up to 37±0.5°C. Then, the mixture was paddled in a mixer at 100rpm. The results are shown in Table 4 and Figures 2.

Table 4: Ratios (%) of the tamsulosin released from the formulations

in pH 6.8 hydrochloric acid solution.

Time (hours)	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6	Example 7	Conventional
0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.50	51.18	37.61	69.90	20.97	27.01	18.14	18.32	15.14
1.00	70.33	52.41	77.54	37.82	42.23	40.29	26.47	31.16
2.00	84.65	65.80	89.18	56.99	56.76	53.24	39.14	50.29
4.00	91.45	76.67	91.76	77.88	76.15	65.88	51.06	71.50
6.00	95.68	85.87	91.10	90.38	85.73	70.35	59.15	82.68
10.00	97.57	91.46	92.66	98.95	92.34	76.71	65.87	91.34
16.00	97.93	94.90	91.47	101.38	96.69	82.10	72.14	92.47

According to Table 4 in view of Fig. 2, all tamsulosin formulations tested showed equal quantity, including conventional sustained release tamsulosin formulation.

Accordingly, the foregoing examples illustrated the following advantages of the sustained release tamsulosin formulations of the present invention:

1. In the process present invention, the use of a microsphere forming agent as a lubricant was surprisingly found to solve the problem resulted from the glue-like status of an acrylic acid polymer or acrylic acid copolymer kneaded under a high temperature.

2. Sustained release tamsulosin formulations of the present invention was found surprisingly to exhibit prolonged ingredient-releasing efficacy. Patients can benefit from a reduction in the frequency of taking such formulations.

Various modifications and variations of the present invention will be recognized by those persons skilled in the art without departing from the scope

and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention, which are obvious to those skilled in the art, are intended to be within the scope of the following claims.